Exhibit 18

Cardiac Sarcoidosis

A Pathology-Focused Review

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● ***Context.***—**Sarcoidosis is a granulomatous disease of unclear etiology. It is not commonly fatal, but when sarcoidosis is fatal, it is most often from cardiac involvement and when sarcoidosis involves the heart, it frequently causes death. The disease presents diagnostic challenges both clinically and histologically.**

Objectives.—**To review the histology of cardiac sarcoidosis and the histologic differential diagnosis of cardiac granulomatous disease and to review the epidemiology and gross pathology of cardiac sarcoid as well as discuss current controversies, clinical diagnostic criteria, and proposed mechanisms of pathogenesis.**

Data Sources.—**We reviewed the literature searchable on PubMed as well as selected older studies revealed by our review of the recent literature. Photographs were taken from cases on file at the University of Pittsburgh Medical Center (Pittsburgh, Pennsylvania) and Columbia University Medical Center (New York, New York).**

Conclusions.—**Sarcoidosis is a focal or disseminated granulomatous disease that likely represents the final common pathway of various pathogenic insults in a genetically susceptible host. The type of insult may influence the specific sarcoid phenotype. Controversy still abounds, but many areas of investigation around sarcoidosis are yielding exciting discoveries and bringing us closer to a richer understanding of this puzzling disease.**

(***Arch Pathol Lab Med.*** **2010;134:1039–1046)**

Sarcoidosis is an aggressively studied systemic granulomatous disease that has been a source of considerable controversy due to its unclear etiology and diverse presentation. It has been aptly described as a disease that causes immense anxiety in both the sufferers and their doctors.[1] Sarcoidosis was first reported as a clinicopathologic entity in the mid-19th century by Jonathon Hutchinson, a prominent dermatologic surgeon who appreciated persistent skin lesions on one of his patients.[2] Various case reports were published over time, with Schaumann ultimately tying together the fairly heterogeneous case reports as one systemic, nonmalignant, nontuberculoid granulomatous disorder in 1914.[3] By 1929 it was demonstrated by Bernstein et al[4] that sarcoidosis could involve the heart. Clinically relevant cardiac sarcoidosis has a variable incidence depending on the population studied,[5] but among fatalities from sarcoidosis cardiac involvement is likely responsible for 50% of cases.[6] There are, however, some populations in whom respiratory demise is a more common cause of death.[7] It is estimated that overall, sarcoidosis is fatal in 1% to 5% of cases.[8]

Accepted for publication September 30, 2009.

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The authors have no relevant financial interest in the products or companies described in this article.

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This review includes interesting issues and current controversies surrounding the etiology of sarcoidosis, clinical and laboratory manifestations of cardiac sarcoid, gross and microscopic pathology of cardiac sarcoid, utility of the myocardial biopsy, and histologic differential diagnostic considerations of cardiac sarcoid.

EPIDEMIOLOGY

The incidence of sarcoidosis varies greatly by ethnic group and region. Incidence is 3 to 20 per 100 000 for whites and 35.5 to 80 per 100 000 for blacks.[9] Scandinavian populations have been reported as having higher prevalence than other whites.[10] The disease most commonly presents in adults younger than 40 years.[8]

The incidence of cardiac sarcoid also varies by ethnic group, as well as by the type of study performed, with autopsy studies of patients dying of sarcoid being heavily weighted toward cardiac involvement. Studies based on clinical findings in known sarcoid patients are likely to quote a prevalence of cardiac involvement in 5% to 10%.[11] However, a recent American study investigated 62 outpatients with documented sarcoidosis but without documentation of cardiac sarcoid. They asked about cardiac symptoms and performed noninvasive tests (simple electrocardiography, Holter monitoring, and transthoracic echocardiography). Any patient who reported symptoms or had an abnormal study was sent for cardiac magnetic resonance imaging or positron emission scanning. The results showed that almost 40% of outpatients with documented sarcoid had cardiac sarcoid. Of these, slightly more than half were asymptomatic.[12]

Cardiac sarcoid is most common among older, female Japanese sarcoid patients who have been purported to

have cardiac involvement at a rate of almost 80%.[5] An excellent American autopsy series from 1978 showed that of patients autopsied with a diagnosis of sarcoidosis, 27% had cardiac sarcoid. Of these, two thirds had clinically significant cardiac disease.[13] Although myocardial fibrosis is nonspecific, it can sometimes be the only manifestation of cardiac sarcoid. This series did not count myocardial fibrosis as evidence of cardiac involvement, so it likely underestimated the true prevalence. The 1952 case series by Longcope and Freiman,[3] which included 92 autopsies at The Johns Hopkins Hospital (Baltimore, Maryland) and Massachusetts General Hospital (Boston) and culled from the literature, found a 20% prevalence of cardiac involvement in patients who were found at autopsy to have sarcoid lesions, which may or may not have been contributing factors to death. From a different perspective, of autopsies done on patients with sudden cardiac death, but without coronary arterial occlusion, granulomatous disease consistent with cardiac sarcoidosis was found in 10 of 184 hearts.[14]

Sarcoidosis is a disease that exhibits numerous genetic associations. These are heterogeneous and vary by population studied, but most of the associations relate to HLA class II molecules.[9] It is possible that genetic susceptibility to sarcoid is dependent on various interacting polymorphisms.[15] Polymorphisms in tumor necrosis factor α and HLA class II genes have been linked to the development of cardiac sarcoid, although it is unclear if the association is particularly specific or strong.[16] It is likely, although not yet fully established, that the genetic basis for cardiac sarcoid is heterogeneous.

ETIOLOGY

The etiology of sarcoidosis remains a mystery, and this is perhaps the greatest source of controversy regarding the disease. Genetic, environmental, infectious, and immune dysregulation etiologies have all had proponents.[17] Virtually all proponents of each etiologic theory acknowledge a role for genetic predisposition. Data from A Case-Control Etiologic Study of Sarcoidosis[18] (ACCESS) indicated a relative risk of 4.7 for parents and siblings of sarcoid patients. Interestingly, white families had a much higher relative risk than black families, 18.0 versus 2.8, respectively. The evidence is not, however, supportive of the idea that sarcoidosis is a purely genetic disease and it is necessary to consider that sarcoidosis may be a disease with heterogeneous triggers in a susceptible host. This possibility is left open by the previously referenced joint statement of the American Thoracic Society, the European Respiratory Society, and the World Association of Sarcoidosis and Other Granulomatous Disorders,[7] which defined sarcoidosis as being a multisystem disorder of unknown cause(s). Heffner[19] recently made the bold assertion that, by reason of logic, sarcoid must be caused by a foreign particle that is too small for us to discern with our current technologies or a nanoparticle. A cause indiscernible with currently available technology cannot be refuted but, by the same token, cannot be proven either. The infectious agents most often cited as possible etiologies include mycobacteria, propionbacteria, *Borrelia burgdorferi*, *Rickettsia helvetica*, and human herpes virus 8.[20] It has also been proposed that bacterial antigens that remain following successful immune clearance of infection are the most likely cause. A recent study used proteomic techniques to search for a bacterial antigen in sarcoid tissues without an a priori hypothesis about what they expected to find. They discovered the mycobacterial antigen *Mycobacterium tuberculosis* catalase–peroxidase protein in slightly more than half of their samples.[21] Nanobacteria have also been hypothesized as an etiologic cause of sarcoidosis.[22] In 2007 a small study demonstrated a dramatic response when antifungal therapy was added in sarcoid patients whose disease was resistant to standard corticosteroid therapy alone.[23] Other groups have demonstrated a beneficial effect of tetracycline-type antibiotics in sarcoidosis, although a possibility that the authors suggest is that this could be primarily derived from the antiinflammatory properties of such drugs.[24]

A case can be made for many agents as etiologic factors in the development of sarcoidosis. A 2006 study found that having one sibling in a family with sarcoidosis greatly increased the odds that another sibling would have it, but the affected siblings had a paucity of shared clinical traits.[25] A possible explanation for this is that the siblings shared a genetic susceptibility to sarcoidosis, but different agents precipitated it in different individuals. Different eliciting antigens may produce a different distribution of disease. This hypothesis is supported by a recent study examining environmental exposures and sarcoidosis that demonstrated that certain environmental exposures (wood burning and organic agricultural dusts) were more likely to be associated with sarcoidosis confined to the lungs than with systemic sarcoidosis.[26]

Some proposed etiologies certainly seem less likely. For instance, an argument against pure immune dysregulation or autoimmunity is that cardiac sarcoidosis is known to recur in recipients of heart transplants despite the allograft likely having different immunogenic antigens.[27,28] Additionally, cardiac sarcoid has been transmitted via transplantation.[29] These results seem to imply both an innate susceptibility and an exogenous trigger. It also seems unlikely that there is any one, specific infectious trigger. The failure to isolate and identify a microorganism from the granulomas of sarcoidosis is strong evidence that it does not have one clear infectious etiology.

Sarcoidosis may, therefore, be a final common pathway of granulomatous disease caused by a heterogeneous group of agents in a genetically susceptible patient.[30]

Mechanistically, the formation of the characteristic epithelioid granuloma is thought to be mediated by cytokines from mononuclear phagocytes, lymphocytes, antigen-presenting cells, and others. In the 1990s Moller et al showed that the cytokines primarily responsible for the granulomatous inflammation of sarcoid were primarily of the T_H1 variety (interleukin [IL]-2, interferon γ, IL-12) and that there was a paucity of T_H2 signals (IL-4, IL-5).[31,32] Recently, an interesting study was performed on a patient with isolated cardiac sarcoidosis. This study demonstrated that early in the course of disease the cytokine milieu did indeed represent a T_H1 type response (high IL-2, IL-12) associated with numerous granulomas on endomyocardial biopsy. One year later, a shift to a T_H2 type (thought to be antiinflammatory) response had occurred (IL-4, IL-5, IL-10, IL-13). This shift coincided with the disappearance of cardiac granulomas on biopsy.[33] A similar shift has been observed in the peripheral blood of patients with pulmonary sarcoid.[34]

CLINICAL FEATURES

There have been numerous clinical and pathologic studies published regarding cardiac sarcoidosis. Predict-

ably, clinical disease burden has been closely tied to the extent of myocardial infiltration at autopsy.[13] Sudden cardiac death, ventricular arrhythmia, atrial arrhythmia, other conduction system disease, congestive heart failure, papillary muscle dysfunction, mitral insufficiency, myocardial infarction, ventricular aneurysm, cor pulmonale, and pericardial effusion can all be presentations of cardiac sarcoidosis.[13,35,36] There is a case report of an atrial mass being a manifestation of cardiac sarcoid.[37] Roberts et al[36] published a thorough autopsy series in 1977 that summarized their experience with sarcoid patients as well as reported autopsy data. Of 89 autopsied sarcoid patients with cardiac dysfunction that could not be explained by other causes, two thirds died of sudden cardiac death and approximately one fourth died of congestive heart failure. This series also suggested that cardiac sarcoid patients generally did not have clinically significant disease in other organ systems. However, more recent studies have not supported this as a valid trend.[13,38] A 2004 series of 41 patients with cardiac sarcoid reported congestive heart failure as the most common clinical sign. Seventeen of 41 had New York Heart Association 2 to 4 functional status. Twenty-four of 41 had New York Heart Association 1. Seven of 41 had arrhythmias. The most common was atrioventricular block, most frequently type 1 heart block, followed by complete heart block and type 2 heart block. Three patients had ventricular arrhythmias.[5] This study was unique, however, in that the patients had a remarkably benign outcome. Grossly, the hearts of patients with sarcoidosis-associated heart failure often display a dilated cardiomyopathy (DCM). In a study of more than 100 patients undergoing left ventriculoplasty for idiopathic DCM, 7% were found to have previously undiagnosed sarcoid.[39] This is an important clinical distinction as it affects not only treatment but also survival. A Japanese study demonstrated a 37% 5-year survival in a cardiac sarcoid cohort when compared with a 64% 5-year survival in a idiopathic DCM cohort with similar New York Heart Association class and ejection fractions.[40] A Dutch series recently reported that of 19 patients with symptomatic cardiac sarcoid, 4 died and 9 required pacemaker and/or implantable cardioverter-defibrillator within 1.7 years. When sarcoidosis is fatal, cardiac involvement is a likely cause of death. Furthermore, when cardiac sarcoid is present, it is commonly fatal, with some series showing up to 50% mortality.[38]

Serum markers may prove useful in diagnosis and monitoring of systemic sarcoidosis. It is well established that serum angiotensin-converting enzyme and lysozyme may be elevated in sarcoidosis, but their diagnostic utility is unclear and controversial due to low specificity and availability. Hypercalcemia may also be present. This is a nonspecific finding thought to represent the production of calcitriol by activated macrophages in the granuloma.[41] IL-6 is elevated early in the disease.[10] Serum IL-12 and interferon γ have also been noted to be increased in systemic sarcoidosis.[42] IL-10 may be a helpful ancillary marker of disease burden. One study showed that cardiac sarcoid sufferers had IL-10 levels of more than 23 pg/mL compared with 2.1 pg/mL for healthy controls and 14.9 pg/mL for idiopathic DCM patients.[43] Interleukin levels are not, however, readily available in most clinical laboratories so they may have to become more widely available before they can be clinically useful.

Another study was recently published that compared inflammatory cytokines in cardiac sarcoid patients with those found in DCM patients. This was evaluated by measuring messenger RNA levels from cardiac tissue rather than quantifying serum cytokines levels. They found much greater levels of IL-1, IL-2, IL-12p40, IL-15, and interferon in the sarcoid patients.[44] This study, and the one mentioned in the preceding paragraph, could perhaps have been more helpful to those with an interest in cardiac sarcoid if they had included noncardiac samples from a group of patients with extracardiac sarcoid because it would be interesting to see if the cytokine profile was different in the two disease states. In a small but exciting study, the same group that performed the previously referenced tissue messenger RNA experiments discovered an analyte that may prove to be of great utility in the diagnosis of sarcoidosis and, specifically, cardiac sarcoid. They found serum myeloid-related protein complex (MRP8/14, an established inflammatory marker) levels to be elevated in sarcoidosis patients compared with healthy controls. Most importantly for this subject, patients with proven cardiac sarcoidosis had significantly higher levels than noncardiac sarcoid patients or idiopathic DCM patients.[45] This offers great promise because cardiac sarcoidosis presents a significant diagnostic challenge. It is also important to note that MRP8/14 may prove to have value in elucidating the pathogenesis of cardiac sarcoid.

The joint statement of the American Thoracic Society, the European Respiratory Society, and the World Association of Sarcoidosis and Other Granulomatous Disorders suggests that sarcoid patients with cardiac dysfunction, electrocardiographic abnormalities, or thallium 201 imaging defects should be presumed to have cardiac sarcoid even if there is no further evidence for diagnosis.[7]

The Japanese Health Ministry has issued guidelines for diagnosis of cardiac sarcoid.[10] It proposes that the diagnosis can be made solely by histologic demonstration of noncaseating, epithelioid granulomas in the heart. If that is not possible, it provides a schema for making the diagnosis on clinical characteristics and imaging.

GROSS AND MICROSCOPIC PATHOLOGY

The cardiovascular system is the third most frequently involved organ system in autopsy studies on patients with sarcoidosis following the lymphoid and respiratory systems.[38] Grossly the granulomatous lesions of cardiac sarcoidosis can appear as yellow, white, tan, light brown, or grey irregular tumorlike infiltrates[36] (Figure 1). In the heart, the myocardium of the left ventricular free wall is the most common location of sarcoid granulomas, followed by the septum, right ventricle, and atria.[36] The disease also commonly affects the cardiac conduction system.[46] The pericardium and endocardium (including valvular endocardium) can also demonstrate sarcoid granulomas, but these appear to be most commonly extensions of myocardial lesions (Figure 1).[36]

Although there is no pathognomonic finding to differentiate a sarcoidal granuloma from a granuloma of another cause, some features favor a granuloma being sarcoidal. The granulomas of sarcoidosis are typically tight, naked, nonnecrotizing, and epithelioid[47] (Figure 2). This criterion is not entirely reliable, however, as early sarcoidal granulomas are not tightly cohesive and may have abundant lymphocytes (Figure 3). Over time, sarcoi-

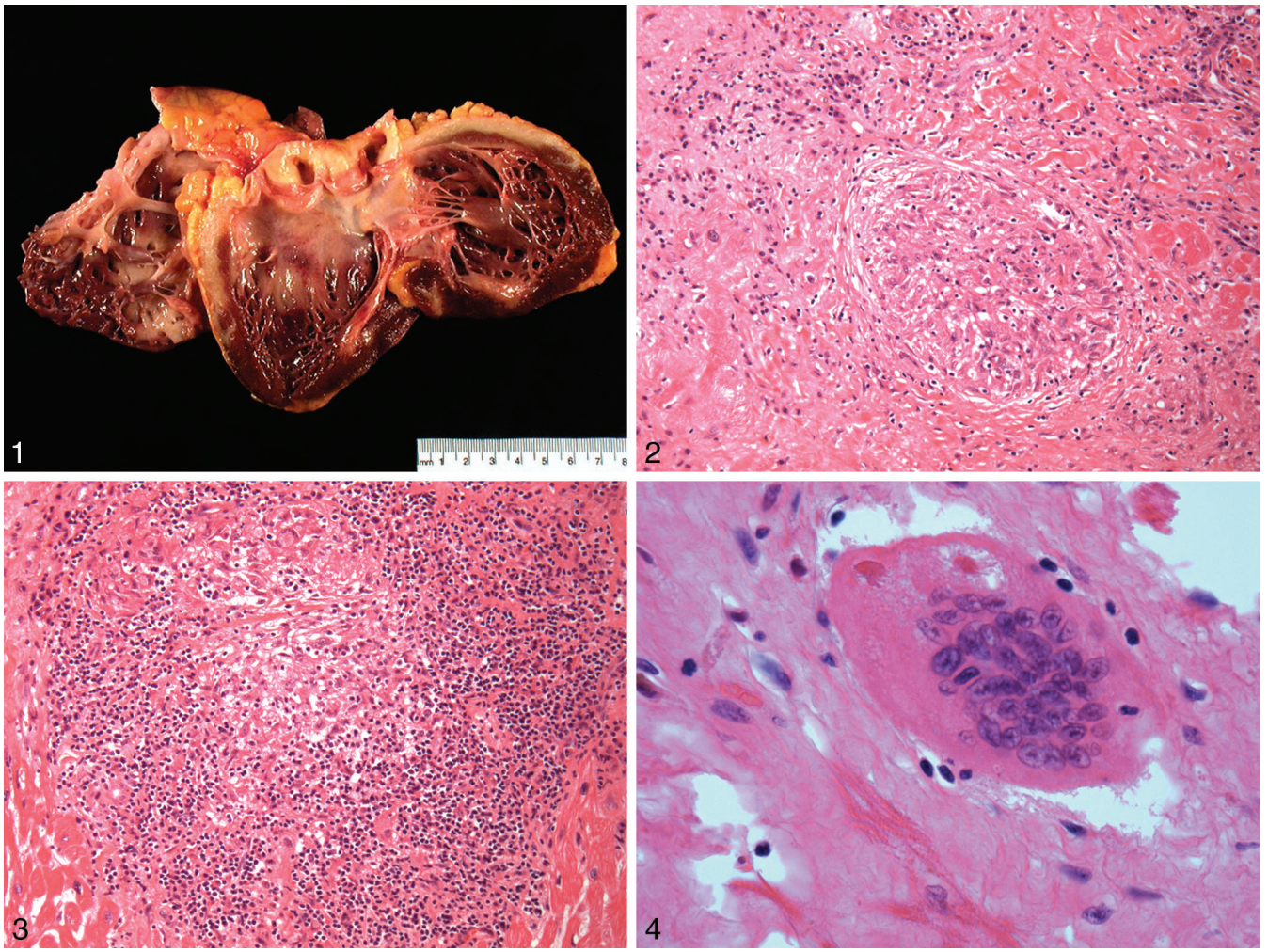


Figure 1. *Heart of a patient who underwent transplantation showing advanced tan to yellow-white fibrotic areas in endocardium, myocardium, and epicardium, with a gradient of involvement, more severe toward the base of the heart. Note the heavy involvement of the epicardium in the anterior left ventricle (upper right of the picture) and endocardium of the right ventricle (lower left of the picture).*

Figure 2. *Low-power view of a typical tight, naked, nonnecrotizing and epithelioid granuloma in the myocardium of an explanted heart from a 43-year-old man with sarcoidosis and heart failure (hematoxylin-eosin, original magnification ×10).*

Figure 3. *Low-power view of less typical, looser granuloma with rare giant cells at the periphery and surrounding lymphoplasmacytic infiltrate in the myocardium of the same patient (hematoxylin-eosin, original magnification ×10).*

Figure 4. *High-power view of an asteroid body within the multinucleated giant cell in the top right area above the nuclei. Note the stellate shape and the cytoplasmic clearing. Also note the nuclei are clustered in a configuration more commonly thought to represent a foreign body–type giant cell (contrast to Figure 5 shown on next page) (hematoxylin-eosin, original magnification ×40).*

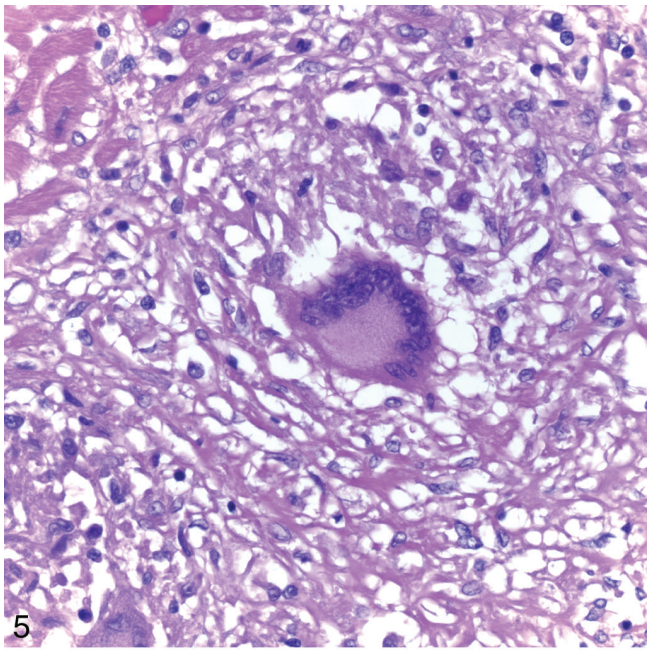
dal granulomas become more compact and come to have less of a rim of lymphocytes.[48] The presence of organisms effectively rules out sarcoid.

The macrophages within sarcoid granulomas tend to become epithelioid and form multinucleated giant cells. Initially, the multinucleated giant cells are more commonly foreign body type (with haphazardly arranged nuclei) (Figure 4). Later, they are more commonly Langhans type (with peripherally arranged nuclei) (Figure 5). The giant cells may contain cytoplasmic inclusions, particularly Schaumann bodies or asteroid bodies (Figures 6 and 4, respectively).

Schaumann bodies are oval, concentrically laminated intracellular inclusion bodies consisting of calcified proteins in giant cells ranging from 25 to 200 μm[49] (Figure 6). Their presence supports the diagnosis of sarcoidosis (approximately 70%–88% of sarcoid cases versus 10% of infectious granulomatous diseases); however, it must be remembered that other nonsarcoid granulomas can also have Schaumann bodies, and certainly not all cases of sarcoid will have them.[48–50] Some claim that Schaumann bodies are nearly as common in berylliosis as in sarcoidosis.[51]

Asteroid bodies are stellate-shaped inclusion bodies found in multinucleated giant cells, generally within a cytoplasmic clearing (Figure 4), thought to be made of noncollagenous filaments and myelinoid membranes that stain with anti-ubiquitin antibodies.[49] The asteroid body is also suggestive but not specific for sarcoid.[49] They are also known to occur with tuberculosis, histoplasmosis, and other granulomatous diseases.[52] Furthermore, asteroid bodies are found in only 2% to 9% of sarcoid tissues, so their presence can only rarely help make the diagnosis.[48]

As cardiac sarcoidosis progresses, the granulomatous inflammation elicits a repair response with scarring. This



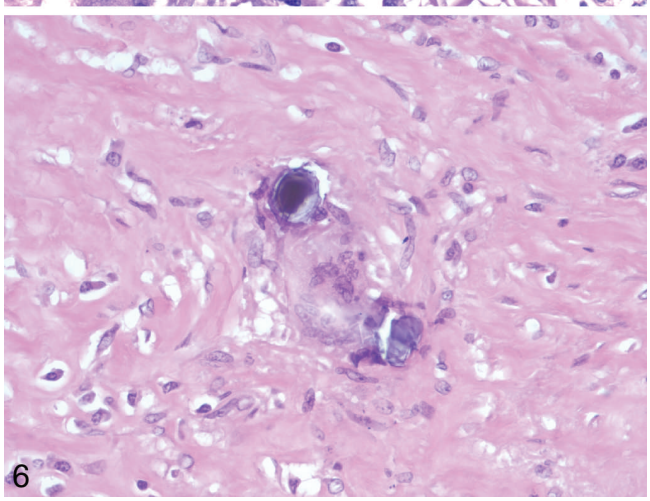


Figure 5. *High-power view of a single granuloma involving the myocardium. Note the rimming of the nuclei (Langhans-type giant cell) (hematoxylin-eosin, original magnification ×40).*

Figure 6. *High-power view of a typical Schaumann body, oval-shaped and with concentrically laminated intracellular inclusion body consisting of calcified proteins within a giant cell (hematoxylin-eosin, original magnification ×40).*

differs from the scarring of myocardial infarction by being randomly distributed throughout the muscle rather than being maximal in the subendocardial region and extending out.[38]

In summary, various features including tight, naked, nonnecrotizing, epithelioid granulomas without a great deal of lymphocytic inflammation; Langhans-type giant cells with or without Schaumann bodies and asteroid bodies; and the presence of patchy fibrosis can all help to make the diagnosis. However, they must all be considered as part of a whole, as none is truly pathognomonic.

HISTOLOGIC DIFFERENTIAL DIAGNOSIS

Endomyocardial biopsy can provide a definitive diagnosis of cardiac sarcoidosis but has low sensitivity due to the patchy distribution of granulomas and lower incidence of disease in the right heart (more accessible for biopsy) compared with the left heart and septum.[53] In 27 patients with clinically diagnosed cardiac sarcoidosis, only 7 were found to have evidence to support the diagnosis on biopsy. This group had a poorer survival rate, presumably due to greater disease burden.[54] Other investigators have demonstrated greater sensitivity in known sarcoidosis patients with presumed cardiac involvement (4 of 8 patients).[55]

The primary histologic differential diagnosis for cardiac sarcoidosis includes giant cell myocarditis, idiopathic (nonspecific) granulomatous myocarditis, tuberculous myocarditis, fungal myocarditis, and Whipple disease. A broader histologic differential would include systemic lupus erythematosus, acute rheumatic carditis, rheumatoid nodules, Takayasu disease, Wegener granulomatosis, giant cell arteritis, syphilis, Erdheim-Chester disease, and ischemic cardiomyopathy.[5]

The two entities at the top of the histologic differential diagnosis for cardiac sarcoidosis are idiopathic granulomatous myocarditis and idiopathic giant cell myocarditis. Idiopathic granulomatous myocarditis is characterized by noncaseating (nonnecrotizing) granulomas in the heart without granulomas in other organs. It is distinguished from cardiac sarcoidosis solely by the absence of extracardiac granulomatous disease. Of course, this could be regarded as sarcoidosis limited to the heart and this is precisely what some pathologists, and some studies, do. In a study comparing cardiac sarcoidosis to idiopathic giant cell myocarditis, two thirds of the cardiac sarcoidosis cases had no evidence of extracardiac involvement.[56] Obviously, if one regards noncaseating granulomatous disease of the heart without extracardiac involvement as cardiac sarcoidosis, idiopathic granulomatous myocarditis disappears as an entity.

Idiopathic giant cell myocarditis is characterized by an infiltrate of eosinophils, lymphocytes, macrophages, and giant cells associated with myocyte necrosis. The macrophages are not epithelioid and do not aggregate into granulomas. The lack of granulomas is perhaps the single most helpful clue to the diagnosis.[56] Variable numbers of plasma cells, occasional neutrophils, and commonly congestion and edema are also features.[57] Eosinophils are significantly more common in idiopathic giant cell myocarditis and fibrosis is significantly more common in sarcoidosis.[56] Such differences, visible on routine hematoxylin-eosin–stained sections, are generally sufficient to make this differentiation. Immunohistochemistry may be of some help in differentiating idiopathic giant cell myocarditis from cardiac sarcoidosis. The lymphocytes in the inflammatory infiltrates of idiopathic giant cell myocarditis are predominantly $CD8^+$, whereas the lymphocytes in cardiac sarcoidosis are predominantly $CD4^+$.[57]

Infective granulomatous myocarditis is rare. It is almost unheard of without extracardiac disease, particularly in the lungs. Tuberculosis of the heart was identified in 19 of 13 658 autopsies in Cape Town, South Africa, prior to 1975 (1 in every 719 autopsies).[58] All 19 patients had disseminated disease and only 1.8% of the 243 patients with disseminated disease in this study had cardiac involvement. Although the organ involvement of tuberculosis is similar to that of sarcoidosis, the granulomas of tuberculosis are usually necrotizing. The granulomas of tuberculosis commonly have a larger rim of lymphocytes and are less tightly cohesive then those of sarcoidosis. Demon-

strating mycobacteria by stain or culture excludes the diagnosis of sarcoidosis, but this is frequently not possible. In such cases, demonstration of *M tuberculosis* DNA by polymerase chain reaction may definitively establish the diagnosis.[59] Fungal infection of the heart occurs with some frequency in immunosuppressed patients, immunocompromised patients, and neutropenic patients but usually only as part of a disseminated infection and these patients rarely have enough immune function and live long enough to mount a granulomatous response. Even with a granulomatous response, the fungi are generally demonstrable by special stain or culture.[60,61] Whipple disease, infection by *Tropheryma whippelii*, almost always involves the small intestine and mesenteric lymph nodes and causes pericarditis in 75%, endocarditis in 50%, myocardial fibrosis in 10%, and myocarditis in 1% of cases. The macrophages of Whipple disease are generally foamy or granular, with more abundant cytoplasm than those of sarcoidosis, and they aggregate into granulomas in only 9% of cases. Most helpful is that the organisms are usually visible in large numbers in the cytoplasm of the infected cells with periodic acid–Schiff stain.[62,63]

Systemic lupus erythematosus involves the endocardium in more than 50% of patients, the epicardium in more than 30% of patients, and the myocardium in less than 10% of patients (3 of 36 autopsied patients in 1 series).[64] Myocardial involvement takes the form of mononuclear inflammatory cell infiltration, but not granulomas, and myocardial infarction due to vasculitis or accelerated coronary atherosclerosis. The anatomic distribution of cardiac disease, serologic test results, and other clinical features can also help differentiate systemic lupus erythematosus involving the heart from cardiac sarcoidosis.

Acute rheumatic heart disease is commonly a pancarditis involving all 3 layers of the heart. It is manifested by Aschoff bodies, which are discrete, commonly perivascular, areas of fibrinoid degeneration surrounded by lymphocytes, occasional plasma cells, and plump macrophages with their nuclear chromatin clumped in a wavy ribbon resembling a caterpillar (Anitschkow cells).[65] Some of the macrophages in an Aschoff body may become multinucleated giant cells. The Jones criteria for the diagnosis of acute rheumatic fever can be used to help differentiate it from sarcoidosis.

Rheumatoid nodules can occur in the epicardium, myocardium, or endocardium but consist of areas of necrosis surrounded by palisaded histiocytes and fibroblasts without giant cells, histologically very different from the nonnecrotizing granulomas of sarcoidosis. Additionally, they are most commonly in the epicardium or valvular endocardium rather than the myocardium.[66] Both rheumatoid arthritis and sarcoidosis generally involve extracardiac organs and the clinical manifestations of disease in these other organs can also make it easy to differentiate rheumatoid arthritis involving the heart from cardiac sarcoidosis.

Takayasu disease involves the coronary arteries in 15% of patients, typically at the ostia in the aorta or in the proximal portions, and myocardial involvement takes the form of myocardial infarction.[67] Takayasu disease is an arteritis; it is granulomatous but typically necrotizing. The epidemiologic and clinical features of Takayasu disease and sarcoidosis are also quite different and, thus, diagnostically helpful. Wegener granulomatosis is a disease of the upper and lower respiratory tracts and kidneys. It only rarely involves the heart and then the characteristic extracardiac involvement, especially with demonstration of antiproteinase 3 (diffuse cytoplasmic antineutrophil) antibodies, can ease the differentiation.[68] Giant cell arteritis occasionally involves the coronary arteries and myocardial involvement takes the form of myocardial infarction. The arteritis is typically granulomatous with necrosis involving the region of the internal elastic lamina. Like the other entities in the expanded differential diagnosis, giant cell arteritis has epidemiologic and clinical features that help distinguish it from cardiac sarcoidosis. Giant cell arteritis can be differentiated from necrotizing sarcoidal angiitis by the lack of granulomatous inflammation in the myocardium outside of the coronary arteries, the lack of granulomatous inflammation in other organs outside of the arteries, and the demographics of the patient because giant cell arteritis is primarily a disease of elderly white women, unlike sarcoidosis.

Tertiary syphilis commonly involves the ascending aorta and aortic root, where it may impinge on the coronary ostia causing myocardial infarction. Tertiary syphilis can cause gummas, which are discrete areas of coagulative necrosis with surrounding macrophages, fibroblasts, lymphocytes, and plasma cells. Gummas are exceedingly rare in the heart except in congenital syphilis. Spirochetes are generally difficult to demonstrate in gummas. The epidemiologic and clinical features of tertiary syphilis are also helpful in differentiating it from cardiac sarcoidosis, and chief among these is the current rarity of tertiary syphilis.[69]

Erdheim-Chester disease is a rare non–Langerhans cell histiocytosis, sometimes referred to as lipoid granulomatosis, most commonly involving bone and organs close to bone such as the pituitary and eyes. It can involve the heart, but it features foamy macrophages rather than the epithelioid macrophages characteristic of sarcoidosis and the occasional giant cells in it are Touton type rather than Langhans or foreign body type.[70] Other histocytic proliferative disorders, such as juvenile xanthogranuloma, rarely involve the heart.

Genetic conditions, such as Gaucher disease, Niemann-Pick disease, and the hyperlipidemias, can involve the heart but with foamy (or at least not epithelioid) histiocytes and with manifestations in other organs that greatly aid differentiation from sarcoidosis.

Ischemic cardiomyopathy is characterized by sufficiently large old myocardial infarctions to be associated with heart failure. The lack of granulomatous inflammation and the presence of severe coronary atherosclerosis generally make it easy to differentiate ischemic cardiomyopathy from cardiac sarcoidosis, although they may coexist. Occasionally patients have myocardial scarring with neither inflammation nor coronary artery disease. Some of them may have ''burn-out'' cardiac sarcoidosis, but without other evidence, this diagnosis should not be made.

CONCLUSION

Sarcoidosis is a focal or disseminated granulomatous disease, which likely represents the final common pathway of various pathogenic insults in a genetically susceptible host. Although fairly rare, cardiac sarcoid is one of the possible manifestations that clinicians must be most vigilant about due to its high risk of causing fatal

arrhythmias or congestive heart failure if untreated. Endomyocardial biopsy can make the diagnosis, but its sensitivity is limited by the patchy myocardial distribution of the granulomas. Although not yet established, serum markers are an exciting area of investigation.

To date, we do not know what predisposes some sarcoid patients to develop cardiac sarcoid. Genetic studies are beginning to provide answers to that question, but more work remains. An exciting idea is that the type of antigenic stimuli may influence the development of different sarcoid phenotypes, including cardiac sarcoid.

Unfortunately, one of the ways cardiac sarcoidosis is commonly diagnosed still remains the autopsy, but this can be of great benefit for both families and medical staff. An autopsy performed by one of the authors of this review revealed cardiac sarcoidosis as the cause of an unexpected sudden death. In addition to the great intrinsic value of the autopsy (particularly in cases of unexpected sudden death), this particular case had the additional benefit of converting the widow from considering a malpractice lawsuit against her husband's doctor to becoming an advocate for the study of sarcoidosis, creating the Heart of Gold Foundation for Sarcoidosis (www.heartofgoldgd.org, last accessed August 17, 2009).

We would like to thank Charles C. Marboe, MD, Department of Pathology and Cell Biology, Columbia University Medical Center (New York, New York) for allowing us to review and take photographs from his case files, as well as for sharing his insights on this disease.

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